

Genetic Research on Alcohol and Drugs: From Abstinence to Dependence

Ethics of Genetics in Research
May 19, 2006



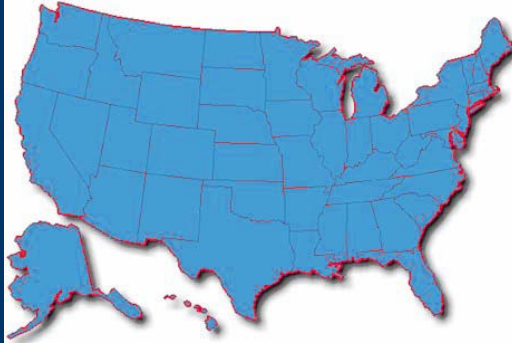
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Dependence Syndrome (Edwards and Gross, 1976)

- The concept: impaired control of substance use despite severe external consequences
- A combination of physiological and psychological processes
- Defined by specific diagnostic criteria shown to be reliable and valid
- Dependence symptoms differ from consequences of heavy use

National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) 2001-2002



- National sample
- N= 43,093
- Residents of households & group quarters
- Oversampled Blacks, Hispanics, adults 18-24
- DSM-IV diagnoses
- <http://niaaa.census.gov>

Alcohol and Drug Dependence

- Lifetime prevalence in the general population
 - Alcohol Dependence 12.5%
 - Drug Dependence 2.5%
- Risk also influenced by environmental factors
 - Early stressful experience, e.g., child abuse
 - Peer groups, laws, pricing, marketing
 - Religiosity, type of religion

Twin studies



- Compare concordance in MZ and DZ twins
- Suggest that genetic heritability a substantial component of risk for alcohol, drug dependence
- More variable heritability for use and heavy use
- Assumption that initiation and dependence have somewhat different causes

Pharmacokinetics, Pharmacodynamics

Approximate Blood Alcohol Percentage
In One Hour

Drinks	Body Weight in Pounds								Influenced
	100	120	140	160	180	200	220	240	
2	0.06	0.05	0.04	0.03	0.02	0.01	0.01	0.01	Impaired
4	0.12	0.09	0.07	0.05	0.04	0.03	0.02	0.02	
6	0.18	0.14	0.11	0.08	0.06	0.05	0.04	0.03	
8	0.24	0.18	0.14	0.11	0.08	0.06	0.05	0.04	
10	0.30	0.23	0.18	0.14	0.11	0.08	0.06	0.05	Legal
12	0.36	0.27	0.21	0.16	0.12	0.09	0.07	0.06	
14	0.42	0.32	0.25	0.19	0.14	0.11	0.08	0.07	
16	0.48	0.36	0.28	0.21	0.16	0.12	0.09	0.08	

Assumes 80% for each hour of drinking. One drink is 1 oz. of 80 proof liquor at 40%, one of beer at 5%, or 4 oz. of wine at 12%.

KNOW YOUR LEGAL LIMIT

In Three (3) states, 20% of Blood Alcohol Content is the primary limit for driving a motor vehicle. There is only one state and one territory where it is considered legal to drive. The figures are calculated as averages. Individuals may vary according to their personal alcohol tolerance. Read in the booklet about the use of emergency, maintenance, health, and performance conditions and also individual factors. In any case, if you're been drinking at all, be careful!

SECRET POLICY IS... DON'T DRIVE AFTER DRINKING

Three Centimeter or Clinical and Drug Issues - © Three Alcohol Beverage Commission

- **Pharmacokinetics:** how the body processes a substance, including rates of metabolism and excretion. This influences how much reaches sites that react or respond to it.
- **Pharmacodynamics:** mechanism of action of a substance at a receptor site, or physiological response to a substance. For psychoactive substances, this involves brain neurotransmitters

- In substance dependence, individual variation in pharmacokinetics and pharmacodynamics are partly under genetic control.
- Understanding the genetic contribution to this variation may lead to improved treatments for dependence.

Addictions are Complex Disorders



The genetic contribution to vulnerability for addiction (generally, or to a specific substance) is hypothesized to involve multiple polymorphisms in different genes.

Alcohol Metabolism via liver enzymes:
2-step process

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Alcohol —————> Acetaldehyde —————> Acetate

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Alcohol
dehydrogenase

ADH2*1 ADH3*1
ADH2*2 ADH3*2
ADH2*3 ADH4

Alcohol Metabolism via liver enzymes: 2-step process

Alcohol —————> Acetaldehyde —————> Acetate

Alcohol
dehydrogenase

ADH1B*1 ADH3*1
ADH1B*2 ADH3*2
ADH1B*3 ADH4

Aldehyde
dehydrogenase

ALDH2*1
ALDH2*2

Alcohol metabolizing genes: ALDH2

- ALDH2*1 allele “normal” – facilitates alcohol metabolism
- ALDH2*2 allele inactive
(Li, 2000; Foroud and Li, 1999)
- Homozygosity for ALDH2*2 almost completely eliminates drinking
- Heterozygosity strongly protective against heavy drinking and alcoholism
- ALDH2*2 found only in Asians

Alcohol metabolizing genes: ADH

- A family of genes located on chromosome 4
- ADH1B (formerly ADH2) most extensively researched
- ADH1B*2 and ADH1B*3 more active than ADH1B*1
- ADH1B effects not as strong as ALDH2*2
- However, also protective against heavy drinking and alcohol dependence

ADH1B*2 prevalence

- Rare (<.05) in most Caucasian groups
- Common in Asian groups
- Intermediate (.19 - .31) in Jewish groups

ADH2 and Continuous Phenotypes Israel, 2000

	<u>ADH2 Genotype</u>			
Phenotype	1*1 (N=38)	1*2 (N=24)	2*2 (N=6)	p value
DEPSEV	0.92	0.46	0.00	0.04
MAXDRINKS	3.89	3.29	1.00	0.02

Hasin et al, Am J Psychiatry, 2002

Hasin et al, Alcohol Clin Exp Res, 2002

Gene-environment interaction suggested in Israel sample

- In native Israelis, ADH1B*2 effects clear
- In Russian Jewish immigrants where prevalence of ADH1B*2 was the same, no ADH1B*2 effect
- Suggested that genetic protection was offset by environmental risk factor
- This served as background for larger gene-environment interaction study now underway in Israel



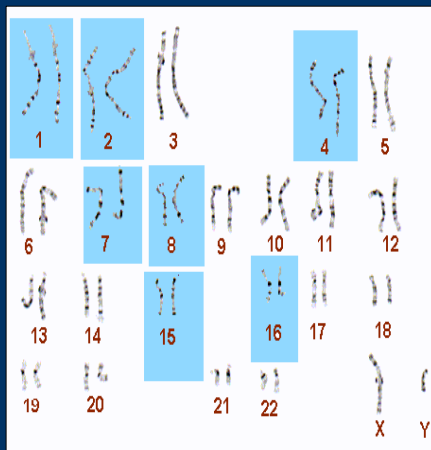
COGA



Collaborative Study of the Genetics of Alcoholism

- Multi-site national study
- Probands identified through inpatient & outpatient treatment programs
- Extended family study design
- DNA collected from 262 families (n=2,282)
- Clinical phenotypes: alcohol and drug use, abuse, dependence, other psychiatric disorders, personality traits
- Endophenotypes: electroencephalographic and event-related potential paradigms to identify neurophysiological markers of risk for the predisposition to alcoholism
- Genome scan: 336 markers; average inter-marker distance 10.5cM

Initial COGA results



- Entire genome assessed for linkage of markers with alcohol dependence using genetic markers spaced at known intervals.
- Linkage found for various alcohol phenotypes on chromosomes 1, 2, 4, 7, 8, 15, and 16 (Reich et al., 1998)

COGA and pharmacodynamics of alcohol dependence

- Gamma-amino butyric acid (GABA)
 - major inhibitory neurotransmitter
 - mediates alcohol effects in animals and humans
 - Alpha2 receptor (GABRA2) polymorphisms on chromosome 4 studied for relationship to alcohol and drug dependence
- GABRA2 receptor results –
 - SNPs strongly related to alcohol dependence
 - SNPs strongly related to brain wave oscillation patterns linked to alcohol dependence (*Edenberg et al., 2004*)

Replications of GABRA2 and Dependence

- Independently replicated - large case-control association study of U.S. substance abuse patients and normals (*Courvart et al., 2004*)
- Independently replicated - large case-control association study of Russian alcoholics and population controls (*Lappalainen et al., 2004*)
- Independently replicated - large case-control association study of German alcoholics and population controls (*Fehr et al., 2006*)
- Association with drug dependence - association found in COGA sample in alcohol dependent cases with comorbid drug dependence (*Agrawal et al., 2006*)
- Association with drug dependence - association found in separate sample of children of COGA participants interviewed at ages 7 - 17 (*Dick et al., 2006*)

ADH genes- new findings

- SNPs in ADH4 associated with risk for alcohol or drug dependence – large U.S. case-control association study (*Luo et al., 2006*)
- SNPs in ADH4 also found in COGA sample - fine gene mapping in COGA sample indicated strong relationship (*Edenberg et al., 2006*)
- Also found in Brazilian alcoholics compared to controls - (*Guindalini et al., 2006*)
- SNPs in ADH1B*3 – protective against alcohol dependence in African Americans in COGA sample (*Edenberg et al., 2006*)

What about drug dependence?

- Studies began more recently
- Results not yet as clear
- Many studies currently underway in the National Institute on Drug Abuse (NIDA) Genetics Consortium
- Includes studies of new phenotype development (e.g. cannabis withdrawal *Hasin et al., under review*)

Pharmacogenetics



- Understanding differential treatment response and individual tailoring of therapy may be aided by identifying genetic factors that affect treatment response.
- Research on this for alcohol dependence currently underway as part of Project COMBINE (Anton et al., JAMA 2006), a study of two medications (naltrexone and acamprosate) and two behavioral treatments (Goldman et al., 2005)

Promises and risks for participants

For participants

- Confidentiality violation risks economic, insurance and social discrimination as in any stigmatized condition, plus additional risk of revealing illegal behaviors in substance abuse studies
- NIH Confidentiality Certificates routinely required
- Understanding of genetic risk for alcohol or drug dependence not yet able to indicate risk clearly, so results not directly useful to research participants

Societal risks and policy issues

Prevention implications

- Young people could potentially be tested before they use alcohol (or drugs) or develop any abuse or dependence symptoms
- This could provide information about the risk of dependence if they decide to use
- Could prevent some cases
- Could also encourage irresponsible use among those testing negative with potentially serious consequences (e.g., car crashes)
- Ethical issues about circumstances of genetic testing, whether voluntary or not

Societal risks and policy issues

Stigmatizing groups

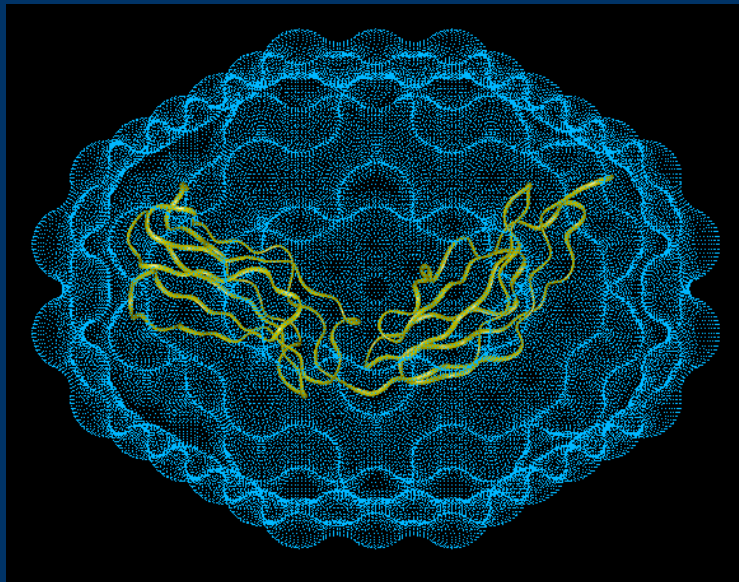
- Genetic differences in alcohol metabolism differ between Asians, African-Americans, Jews, Whites
- Impossible to predict how genetic findings on racial differences will be misunderstood and misinterpreted

Genetic information could lead to:

- Ignoring environmental factors affecting risk for alcohol/drug dependence
- Reduced support for effective policies such as higher legal drinking age
- Overly simplistic “brain disease” interpretation, reducing personal responsibility

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DSM-IV Alcohol Dependence

Maladaptive drinking leading to clinically significant impairment or distress, shown by 3+ of the following in the same 12-month period:

- Drinking more or longer than intended
- Persistent desire or unsuccessful efforts to cut down or stop
- A great deal of time spent on drinking or getting over its effects
- Important activities given up or reduced because of drinking
- Continued drinking despite knowledge of a serious physical or psychological problem
- Tolerance
- Withdrawal, or drinking to avoid or relieve drinking